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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,102	07/11/2003	Edward H. Lin	UTSC:755US	3950

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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,102	LIN ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *3,4 and 15-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/19/03;8/20/04;8/12/05*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-14, species A, claim 2) in the reply filed on February 8, 2006 is acknowledged.

2. Claims 3, 4 and 15-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species and inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 8, 2006.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. Claims 1, 2 and 5-14 will be examined.

Information Disclosure Statement

5. The information disclosure statements (IDSs) submitted on December 19, 2003, August 20, 2004 and August 12, 2005 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 2 and 5-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1, 2 and 5-14 are broadly drawn to a method of diagnosing cancer in a human subject by obtaining a sample comprising cells of the subject, obtaining RNA from the cells, performing quantitative PCR using primers which amplify AC133 nucleic acid and comparing the amount of AC133 amplification product with the amount of amplification product in non-cancer cells, where an increase in the amount of AC133 amplification product in cells of the subject as compared to the amount of AC133 amplification product in non-cancer cells indicates that the subject has cancer. However, as will be further discussed, there is no support in the specification and prior art for the method. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification provides two working examples. In Example 2 (page 29, lines 1-22), RT-PCR was performed on mononuclear stem cells from three patients with colorectal carcinoma

(CRC) and two healthy individuals. The cells from the normal individuals showed no expression of AC133 in the stem cells, whereas the three CRC-affected patients showed AC133 expression. In Example 3 (page 29, lines 25-28; page 30-32), Applicants examined expression of AC133 mRNA in 58 CRC patients in peripheral blood cells, and found correlation between the presence of the AC133 expression and the presence of cancer. However, these examples do not provide support for the claimed method because:

a) the cells examined were not cancer cells, rather, they were mononuclear cells (stem or blood cells) from cancer-affected and cancer-free individuals,

b) there are no examples that expression of AC133 is elevated in mononuclear cells of individuals affected with any other type of cancer,

c) there is no evidence that expression of AC133 is elevated in cancer cells of individuals affected with any type of cancer,

d) there is no evidence that the level of AC133 expression is correlated with tumor burden,

e) there is no evidence that the level of AC133 expression is correlated with tumor relapse,

f) there is no evidence that AC133 in mononuclear cells is elevated only in cases of cancer.

Guidance in the Specification.

The specification provides no evidence that the claimed invention can be practiced, since it is not clear whether any other disease process can result in an increase in the AC133 expression. Further, Applicants provided no evidence that AC133 is expressed in tumor cells and is not expressed in normal cells of any cancer. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

The unpredictability of the art and the state of the prior art

The specification discloses correlation between AC133 expression in stem or peripheral blood mononuclear cells and the presence of colorectal cancer in a group of patients. However, as

can be seen from the prior art, conditions other than cancer cause elevated levels of AC133 in peripheral blood cells and the presence of cancer is not always correlated with elevated expression of AC133 mRNA.

Gill et al. (Circ. Res., vol. 88, pp. 167-174, 2001; cited in the IDS) showed that vascular trauma such as surgery causes an increase in the number of AC133-expressing cells in the blood (Abstract; page 172, second paragraph; page 173). Nakatani et al. (Clin. Exp. Immunol., vol. 131, pp. 536-540, 2003; cited in the IDS) showed that Kawasaki disease involves increase in the number of endothelial progenitor cells expressing AC133 (Abstract; page 536; page 537, seventh paragraph; page 538, second paragraph).

The correlation between presence of cancer in an individual and expression of AC133 mRNA in either the tumor cells or the peripheral blood mononuclear cells (PBMCs) is not unique, i.e., AC133 is not expressed in all tumor cells. For example, only a percentage of brain tumor cells express AC133, as documented by Singh et al. (Cancer Research, vol. 63, pp. 5821-5828, 2003; cited in the IDS). In human brain tumors investigated by Singh et al. only undifferentiated tumors expressed CD133 (Fig. 4), and the percentage of tumor cells expressing CD133 ranged from 3.5 to 46.3 (page 5824, last two paragraphs). These findings are supported by evidence provided for the correlation between expression of AC133 and leukemia. Vercauteren et al. (Cytotherapy, vol. 3, pp. 449-459, 2001; cited in the IDS) examined a relationship between the presence of AC133 in PBMCs and the AML (Acute Myelogenous Leukemia). They found that there was no clear correlation between the AC133 expression ad the presence of leukemia, as some of the leukemia cells were AC133-negative (page 453, second and third paragraph; page 454, second paragraph; page 456, last paragraph; page 457, first paragraph). Finally, Lee et al. (Leukemia Research, vol. 25, pp. 757-767, 2001; cited in the IDS) investigated expression of AC133 in cells of patients with AML and ALL (acute lymphoblastic leukemia) (Abstract). Their results support the conclusions of Vercauteren et al., in that the percentage of cells expressing AC133 ranged from 21 to 89 (page 759, fifth paragraph; Table 4; page 763, fifth and sixth paragraph; page 764, paragraphs 1-3).

Chromosomal aberrations were found with the same frequency in AC133+ and AC133- leukemias (Table 2; page 762, third paragraph). The rate of remission, survival times and clinical outcomes were not statistically different between the AC133+ and AC133- tumors (page 763, second and third paragraph; Table 6).

Therefore, the above references provide the following conclusions: expression of AC133 is not always the result of cancer in a subject, and not all cancer cells or PBMCs from cancer patients express AC133.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this method to cancer diagnosis. First, all possible cancers would have to be examined in population studies to determine whether AC133 is expressed in cancer cells and/or PBMCs. Influence of other diseases and traumas would need to be examined as well. Then association of AC133 expression with tumor burden and tumor relapse would have to be determined for all possible cancers. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the presence of AC133 mRNA expression is correlated with diseases and conditions other than cancer and where AC133 is expressed in some, but not all, cancer cells, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of AC133 expression in cancer cells or PBMCs to diagnose cancer. Thus given the broad claims in an art whose nature is identified as

unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 2 and 5-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2 and 5-14 are indefinite in claim 1. Claim 1 contains the trademark/trade name PCR™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe an amplification process and, accordingly, the identification/description is indefinite.

10. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Teresa E. Strzelecka
Primary Examiner
Art Unit 1637

Teresa Strzelecka
4/12/06